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201-15339

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June 7, 2004

Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

RE: **HPV Chemical Challenge Program**
Response to Comments
AR-201-14392
Chloronitrobenzenes Category
o-nitrochlorobenzene, CAS No. 88-73-3
m-nitrochlorobenzene, CAS No. 121-73-2
p-nitrochlorobenzene, CAS No. 100-00-5

We are pleased to provide the Agency our responses to comments received from EPA and other stakeholders on our referenced HPV Chemical Challenge submission for the Chloronitrobenzenes Category, which you will find attached. We are forwarding responses to the specific comments, along with a revised Test Plan and Robust Summary package.

Thank you for your consideration. Please contact me directly should there be any question related to this submission.

Sincerely,

Donald A. Lederer, CHMM
Product Stewardship Manager

Response to Comments on HPV Challenge Submission

Chloronitrobenzenes Category

CAS Number 88-73-3; 1-chloro-2-nitrobenzene

CAS Number 121-73-3; 1-chloro-3-nitrobenzene

CAS Number 100-00-5; 1-chloro-4-nitrobenzene

EPA Comments

Specific Comments on the Test Plan

COMMENT 1: *Water solubility*. The submitter provided an experimental value of 189.4 mg/L for PNCB, which is adequate for the purposes of the HPV Challenge program. However, the submitter provided calculated values for ONCB and MNCB. According to OECD guidelines, measured (experimental) values need to be provided unless the calculated values are less than 1 µg/L at 25°C. Therefore, the submitter needs to provide a measured water solubility value for at least one of these chemicals (ONCB or MNCB) so the data can be read across to the third chemical. Ideally, measured data should be provided for the chemicals with the lowest and highest solubilities.

RESPONSE: Measured values for the water solubility of all three isomers have been located and included in the Test Plan and new Robust Summaries have been prepared that use the estimation method as supporting evidence for experimental values**.**

COMMENT 2: *Stability in water*. The test plan states that these chemicals are stable in water owing to a lack of hydrolyzable functional groups. This is not strictly correct, as the chlorine atoms in ONCB and PNCB are substantially more labile than in simple chlorobenzenes. However, EPA agrees that hydrolysis of the chlorine substituent is unlikely under normal environmental conditions. The submitter needs to explain its conclusion in robust summary format.

RESPONSE: Robust summaries, based on chemical principles, for the water stability of all three isomers have been prepared and added to the robust summaries. The test plan text and tables have been updated to reflect the more explicit estimation method**.**

COMMENT 3: *Biodegradation*. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program. The submitter needs to correct the description of biodegradation in the test plan (page 15), which states that the Semi-Continuous Activated Sludge (SCAS) tests "followed similar standards for conduct subsequently codified into OECD guideline 301". This type of test was codified into OECD Guideline 302A (modified SCAS test). EPA agrees with the submitter that these chemicals are not readily biodegradable (test plan, page 16).

RESPONSE: The test was corrected to indicate that the SCAS test was representative of the OECD 302 series inherent tests and not the ready tests. Several additional paragraphs of test were added to the test plan pulling together the information from the primary and supplementary tests. The overall conclusion that these materials are not readily biodegradable but are degradable with time was more clearly stated and supporting evidence was presented. No material changes were made in the robust summaries.

COMMENT 4: *Genetic Toxicity*. EPA reserves judgement on the adequacy of the bacterial mutagenesis assays, pending receipt of robust summaries that identify the test compounds by name.

RESPONSE: Chemical names and CAS Registry numbers have been added for all tested substances. Where available, supplier information, lot numbers and purity information has also been added

COMMENT 5: *Reproductive Toxicity*. EPA reserves judgment on the adequacy of this endpoint for ONCB, pending receipt of a revised robust summary that identifies the organs examined for histopathology, and for PNCB, verification of the compound name.

RESPONSE:

The requested information has been added to the robust summaries

COMMENT 6: Ecological Effects *(fish, invertebrates, and algae*) There were several inconsistencies in the test plan. First, Tables 1, 2, and 3 (pp. 11-13) reported that estimation methods were not available for aquatic toxicity endpoints for ONCB or PNCB or for acute fish toxicity for MNCB. Predicted toxicity values, however, were included in the test plan for each of the three isomers for all three aquatic toxicity endpoints. Second, page 17 reports that ECOSAR predictions were reported for daphnids and algae; however,

predictions for fish were also reported. Finally, Table 6 (p. 17) indicates that a 48-hour algal EC50 was estimated for the MNCB. The estimated EC_{50} value, however, was a 96-hour value.

RESPONSE: Thank you for the careful review and finding these inconsistencies. All of these have been corrected in the revised test plan.

Specific Comments on the Robust Summaries

COMMENT 7: Each summary should clearly identify the test substance by the chemical name. Some robust summaries did not identify the test substance at all and others identified the compound only by its acronym. The submitter needs to revise the summaries, especially for the studies that did not identify the test substance.

RESPONSE: The test substance has been identified in all revised robust summaries. As far as possible, the source and purity of the test substance has also been added.

COMMENT 8: *Genetic Toxicity.* Robust summaries for mutagenesis assays in *Salmonella typhimurium* for the need to specify the test material.

RESPONSE: Chemical names and CAS Registry numbers have been added for all tested substances. Where available, supplier information, lot numbers and purity information has also been added. All were checked for accuracy.

COMMENT 9: *Reproductive Toxicity.* A robust summary for a continuous breeding assay in mice exposed to ONCB by gavage needs to identify the organs examined for histopathology and include separate NOAEL fields for systemic and reproductive toxicity.

The submitter needs to identify the test substance in the summary in the PNCB dossier for a two-generation reproductive toxicity assay in rats, which identified the chemical as ONCB under "Test substance" but as PNCB in the results section and PNCB in the reference list. The submitter needs to include separate NOAELs for systemic and reproductive toxicity.

RESPONSE: The ONCB reproductive robust summary was amended to include separate fields for systemic and reproductive toxicity and the reproductive organs evaluated were listed.

In the PNCB summary, the correct test substance identification has been added as has detailed information about the substance used for the two-gen study including purity, lot number and impurities. A separate conclusion has been added clearly stating the

systemic NOAEL and the reproductive NOAEL. The NOAELs in the definitive field section of the robust summary have been corrected to reflect the results and the conclusions.

The PNCB continuous breeding robust summary was also amended similarly.

COMMENT 10: *Developmental Toxicity*. The summary for the ONCB inappropriately used the ">=" symbol rather than the "=" symbol in the NOAEL fields for doses that were not the highest dose levels.

RESPONSE: This inadvertent symbol use was corrected for the ONCB study.

In addition, the PCNB rat developmental toxicity study has been marked as critical and detailed information has been provided about the test substance. Detailed information about the test substance used in the rabbit developmental toxicity study was also included in the robust summary.

COMMENT 11: ECOSAR predictions were reported for each chloronitrobenzene isomer for all endpoints; however, no details on the inputs used to generate the predictions were reported. Also, the robust summaries indicated that the SAR for esters was used for all of the predictions although none of the sponsored chemicals are esters. From independent model runs, it appears that the submitter correctly used the SAR for neutral organics for toxicity predictions for MNCB. However, it is not clear how the submitter determined the predicted toxicity values for the other two isomers.

RESPONSE:

The ECOSAR modeling was run again using SMILES structures as given in the robust summaries for all three isomers. The original ECOSAR were run with the neutral organics model and not the ester model and this typographical error has been corrected. The original modeling was also run allowing the ECOSAR program to estimate the $K_{o/w}$ that was used in the algorithm. The new calculations were run using the measured $K_{o/w}$ and are thus considered to be better estimates. The ECOSAR calculations are "Critical Studies" for the invertebrate and algal endpoints of MNCB and have been added to the other aquatic robust summaries as supporting data. In all cases the methodology and inputs are clearly shown in the robust summaries.

COMMENT 12: *Fish*. Important details missing from one or more summaries included results based on measured concentrations, values for the actual test concentrations, use

and response of controls, mortality data, 95% confidence intervals, statistical methods, and concentration of the solvent (acetone).

RESPONSE:

Ortho: All available information from this study is provided in the robust summary. The ECOSAR calculation has been shown in detail as supporting data.

Meta: All available information from this study is provided in the robust summary. The ECOSAR calculation has been shown in detail as supporting data.

Para: All available information from this study is provided in the robust summary. Exact purity and CASNO of test substance have been added. The ECOSAR calculation has been shown in detail as supporting data.

COMMENT 13: *Invertebrates*. Important details missing from one or more robust summaries included test substance identity and purity, mortality data, and the concentration of the solvent.

RESPONSE:

Ortho: All available information from this study is provided in the revised robust summary. The ECOSAR calculation has been shown in detail as supporting data.

Meta: The ECOSAR determination has been rerun using the measured Kow value and all parameters have been clearly indicated. The supplemental study lack details but all available information is provided in the robust summary for this published study.

Para: All available information from this study is provided in the revised robust summary. The ECOSAR calculation has been shown in detail as supporting data.

COMMENT 14: *Algae*. Important details missing from one or more robust summaries included test substance purity, type of test (e.g., static, semi-static, or flow-through), pH at the beginning and end of the test, water hardness, specific test concentrations (although ranges were provided), type of regression analysis used to determine the EC_{50} values, and which endpoint (biomass, etc.) was reported.

RESPONSE:

Ortho: All available information from this study is provided in the revised robust summary including the method of regression analysis and type of test. Water hardness is

not necessary as this study used a defined media, which is described in the published reference, prepared from deionized water. PH and endpoint have been addressed. The ECOSAR calculation has been revised to reflect the measured Kow value as an input and has been shown in detail as supporting data.

Meta: The ECOSAR determination has been rerun using the measured Kow value and all parameters have been clearly indicated. The supplemental study lack details but all available information is provided in the robust summary for this supporting published study.

Para: All available information from this study is provided in the revised robust summary including the method of regression analysis and type of test. Water hardness is not necessary as this study used a defined media, which is described in the published reference, prepared from deionized water. The initial pH value has been added. The ECOSAR calculation has been revised to reflect the measured Kow value as an input and has been shown in detail as supporting data.

Environmental Defense Comments

COMMENT 15: The sponsor states that there are no known consumer uses of category members and that emissions are minimal. However, no information was provided on environmental releases (air or water) during the production of different products. It seems plausible that the emissions for some uses of the chloronitrobenzenes might be greater than it is for others. While some of these potential releases would likely come from the facilities of Solutia's customers for these chemicals, we encourage the sponsor to provide environmental release data if available for the different uses of the chloronitrobenzenes.

RESPONSE: The commenter is correct. Data are not available to support the conclusion of minimal release to air and water. This conclusion is not an integral part of the HPV Chemical Challenge, thus it has been removed from the Test Plan.

COMMENT 16: The sponsor states that PCNB is the most toxic of the chloronitrobenzenes; however, this statement is not supported by data presented in the robust summaries. For example, all proposed members induce methemoglobinemia and rat acute toxicity data show that MCNB is the most toxic, followed by OCNB and then PCNB. Moreover, inhalation repeat dose studies indicate no difference in the NOEL for OCNB and PCNB. These studies also show that OCNB induces epithelial hyperplasia of the respiratory tract at low doses, whereas PCNB does not cause this effect even at high doses. Mutagenicity studies indicate that OCNB and PCNB are equipotent. Therefore, the

data indicate that PCNB cannot be considered the most toxic of the chloronitrobenzenes. Rather, in our view, rank ordering done for purposes of read-across needs to reflect the actual toxicity values for a given endpoint for the category members. It should also be assumed that any effect caused by any of the proposed category members will occur for all members.

RESPONSE: This conclusion was drawn in the context of relative potency of these isomers to form methemoglobinemia. See Davydova, SG. 1967. A Comparison of the Properties of Nitrochlorobenzene Isomers for the Determination of Their Permissible Concentrations in Water Bodies. Hyg. and Sanit. 32(8):161-166. for a discussion of the relative toxicity of these three isomers

COMMENT 17: The sponsor states that there is an adequate margin of safety for occupational exposures to the chloronitrobenzenes. This is a risk assessment statement and there is inadequate data presented in the test plan and robust summaries to justify it. We also note that inhalation repeat dose studies on OCNB indicate that hyperplasia of the respiratory epithelium and methemoglobinemia are occurring at a dose of 1.1 ppm -- an exposure level quite close to the TLV. This finding does not indicate an adequate margin of safety.

RESPONSE: This risk assessment statement has been deleted, as risk assessment is not an integral part of the HPV program.

Animal Protection Organizations Comments

No responses necessary